

(19)



Europäisches Patentamt  
European Patent Office  
Office européen des brevets



(11) Publication number:

**0 635 254 A1**

(12)

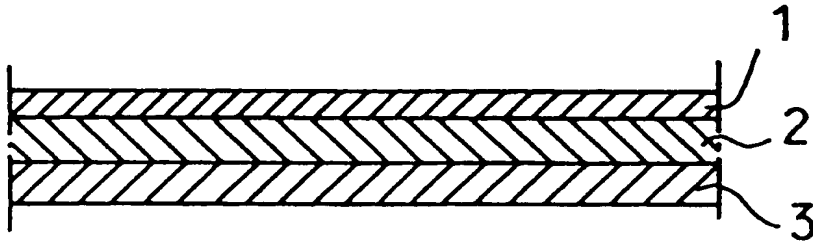
**EUROPEAN PATENT APPLICATION**  
published in accordance with Art.  
158(3) EPC

(21) Application number: **94905826.7**(51) Int. Cl.<sup>8</sup>: **A61J 1/05**(22) Date of filing: **02.02.94**(86) International application number:  
**PCT/JP94/00143**(87) International publication number:  
**WO 94/17772 (18.08.94 94/19)**(30) Priority: **05.02.93 JP 18896/93**  
**06.08.93 JP 195668/93**(43) Date of publication of application:  
**25.01.95 Bulletin 95/04**(84) Designated Contracting States:  
**AT BE CH DE DK ES FR GB GR IE IT LI LU MC**  
**NL PT SE**(71) Applicant: **OTSUKA PHARMACEUTICAL**  
**FACTORY, INC.**  
**115, Aza Kuguhara**  
**Tateiwa**  
**Muya-cho**  
**Naruto-shi**  
**Tokushima 772 (JP)**(72) Inventor: **INOUE, Fujio**  
**240-41,**  
**Oshiro,**  
**Otsu-cho**  
**Naruto-shi,**  
**Tokushima 772 (JP)**Inventor: **IZUMI, Masamitsu**  
**60,****Aza Nanamai,**  
**Tateiwa,**  
**Muya-cho**  
**Naruto-shi,**  
**Tokushima 772 (JP)**Inventor: **KASHIYAMA, Shigetoshi**  
**101,**  
**Aza Nanamai,**  
**Tateiwa,**  
**Muya-cho**  
**Naruto-shi,**  
**Tokushima 772 (JP)**(74) Representative: **Barz, Peter, Dr.**  
**Patentanwälte Dr. V. Schmied-Kowarzik**  
**Dipl.-Ing. G. Dannenberg**  
**Dr. P. Weinhold Dr. D. Gudel**  
**Dipl.-Ing. S. Schubert Dr. P.**  
**Barz**  
**Siegfriedstrasse 8**  
**D-80803 München (DE)**(54) **MULTILAYERED MEDICAL FILM AND DOUBLE-COMPARTMENT CONTAINER.**

(57) A multilayered medical film mainly used for forming a double-compartment medical container and excellent in heat resistance, transparency, flexibility, impact resistance, and easiness in peeling and sealing, which film is composed of: an inner layer formed from a resin mixture composed of an ethylene/ $\alpha$ -olefin copolymer having a density of 0.930-0.945 g/cm<sup>3</sup> and polypropylene, an intermediate layer containing at least one mixed resin layer formed from a resin mixture, in a ratio of 1:5 to 2:1 by weight, of an ethylene/ $\alpha$ -olefin copolymer having a density of 0.920-0.945 g/cm<sup>3</sup> and an ethylene/ $\alpha$ -olefin elastomer having a density of 0.880-0.890 g/cm<sup>3</sup>, wherein the mixed resin layer accounts for at least 85 % of the whole intermediate layer in thickness, and an outer layer formed from an ethylene/ $\alpha$ -olefin copolymer having a density of 0.930-0.945 g/cm<sup>3</sup>.

**EP 0 635 254 A1**

FIG. 1



## TECHNICAL FIELD

The present invention relates to medical multilayer films which are excellent in heat resistance, transparency, flexibility, impact resistance, easily peelable sealing properties, etc. and to medical containers  
5 formed of said films and having a plurality of chambers.

Such medical containers have a plurality of chambers for individually accommodating unstable medical preparations (liquid, powdery or solid preparations) which are likely to change with time when mixed together, and a weak seal portion (easily peelable seal portion) separating the chambers and easily  
10 openable when desired by peeling to mix the medical contents of the chambers.

The term "easily peelable sealing properties" as used herein refers to such properties of a film that the film is capable of selectively forming a strong seal portion which is substantially not openable by peeling or a weak seal portion (hereinafter referred to as the "easily peelable seal portion") which is easily openable by peeling, one of the seal portions being formable by altering the fusing temperature for heat sealing.

## 15 BACKGROUND ART

Films for medical containers are generally formed by polyethylene or polypropylene which has high chemical stability to acids, alkalis, salts, etc. Also known as films for use in forming such medical containers having a plurality of chambers are single-layer or two-layer films having a resin layer which is prepared  
20 from a molten mixture of alpha-polyolefin resins, such as polyethylene and polypropylene, which are different in compatibility.

For example, Unexamined Japanese Patent Publication No. 4671/1990 discloses a single-layer film of resin mixture of two components, i.e., a linear low-density polyethylene and polypropylene, or a single-layer film of resin mixture of three components, i.e., a linear low-density polyethylene, polypropylene and  
25 ethylene-propylene copolymer. A two-layer film is also disclosed which comprises an outer layer of linear low-density polyethylene, and an inner layer of resin mixture of linear low-density polyethylene and polypropylene. In the resin mixtures mentioned, polypropylene has the highest melting point and is used mainly to ensure easily peelable sealing properties.

However, the single-layer film of two-component resin mixture contains in the single-layer forming resin  
30 a large amount of polypropylene which is lower than polyethylene in transparency, flexibility and impact resistance, so that the container prepared from this film is low in usefulness in respect of transparency, flexibility and impact resistance.

Further the problem of nonuniformity of the components is encountered with the single-layer film of three-component resin mixture when the mixture is made into the film. Stated more specifically, the  
35 ethylene-propylene copolymer which is amorphous or low in crystallinity and lowest in melting point is greater than the other two components and especially much greater than polypropylene in fluidity, with the result that the resin components of the film are likely to be present unevenly. It is therefore difficult for the film to effectively exhibit transparency, flexibility and impact resistance which are the outstanding characteristics of the ethylene-propylene copolymer resin. Moreover, it is difficult to uniformly disperse  
40 polypropylene in polyethylene and to form a film which has excellent easily peelable sealing properties, that is, which contains polypropylene as uniformly dispersed therein. The single-layer film wherein the component resins differ greatly in melting point encounter another problem when heat sealed. When the component resin of the highest melting point (polypropylene) starts to melt, the component resin of the lowest melting point (ethylene-propylene copolymer) has been excessively melted to flow in the form of a  
45 liquid, greatly reducing the thickness of the film to be heat sealed. Accordingly, the film is not heat sealable properly to give the desired strength to containers.

On the other hand, the two-layer film disclosed in the above-mentioned publication has slightly higher transparency and flexibility than the single-layer films since a linear low-density polyethylene (L-LDPE) is used for the outer layer, whereas this film is still unsatisfactory. Additionally, the film has a problem in  
50 respect of impact resistance when made into containers, especially when the container is cooled to 5° C or lower. For these reasons, the two-layer film is not satisfactory for medical use and is not suited to use.

Further because much consideration is not given to the heat resistance of these films, containers formed of these films and having a plurality of chambers are likely to give undesirable results. When the container is sterilized with high-pressure steam or hot water under a high-temperature condition (e.g., 121°  
55 C for 20 minutes), the resin present in the film (linear low-density polyethylene or ethylene-propylene copolymer) fails to withstand the sterilizing temperature to melt or foam, deforming or rupturing the container or permitting a leak through the sealed portion. It is further likely that the polyethylene will dissolve out in the form of fine particles. At the easily peelable seal portion providing a partition between the

chambers and rendering the partition easily openable, the linear low-density polyethylene or ethylene-propylene copolymer similarly fails to withstand the sterilizing temperature to melt, consequently increasing the seal strength of the easily peelable seal portion to a level comparable to the strength of the hermetic seal portions (strong seal portions) other than the easily peelable seal portion, hence low usefulness. The sterilization at the temperature of 121° C also lowers the transparency and flexibility which are not negligible items of evaluation since these properties greatly influence the handling of the container at the site of medical treatment.

#### DISCLOSURE OF THE INVENTION

The main object of the present invention is to overcome the foregoing problems and to provide a medical film and a container having a plurality of chambers which are excellent in any of heat resistance, transparency, flexibility, impact resistance and easily peelable sealing properties.

Other features of the invention will become apparent from the following description.

The present invention provides a medical multilayer film characterized in that the film comprises an inner layer, an intermediate layer and an outer layer each made primarily of a polyolefin,

the inner layer being formed of resin mixture of an ethylene-alpha-olefin copolymer having a density of 0.930 to 0.945 g/cm<sup>3</sup> and a polypropylene,

the intermediate layer including at least one resin mixture layer of resin mixture of an ethylene-alpha-olefin copolymer having a density of 0.920 to 0.945 g/cm<sup>3</sup> and an ethylene-alpha-olefin elastomer having a density of 0.880 to 0.890 g/cm<sup>3</sup> in a mixing ratio by weight of 1:5 to 2:1, the resin mixture layer having a thickness of at least 85% of the overall thickness of the intermediate layer, and

the outer layer being formed of an ethylene-alpha-olefin copolymer having a density of 0.930 to 0.945 g/cm<sup>3</sup>.

To give further improved heat resistance to the multilayer film as a preferred mode of the present invention, the intermediate layer has in the middle thereof a layer of an ethylene-alpha-olefin copolymer having a density of 0.930 to 0.945 g/cm<sup>3</sup>.

The container of the invention having a plurality of chambers is prepared from the multilayer film described.

The ethylene-alpha-olefin copolymer for use in the present invention comprises ethylene as the main comonomer and contains a specified proportion of alpha-olefin. The copolymer may be in the form of a random copolymer, block copolymer or graft copolymer.

The ethylene-alpha-olefin elastomer is an ethylene-alpha-olefin copolymer which is amorphous or low in crystallinity.

Examples of useful alpha-olefins for use in the ethylene-alpha-olefin copolymer or ethylene-alpha-olefin elastomer are those having 3 to 12 carbon atoms, such as propylene, 1-butene, 1-pentene, 1-hexene, 4-methyl-1-pentene, 1-heptene, 1-octene, 1-nonene, 1-decene, 1-undecene and 1-dodecene. Among these, 1-butene is suitable for use in the copolymer. Especially, a linear polymer is desirable as the ethylene-alpha-olefin copolymer. The ethylene-alpha-olefin copolymer having a density of 0.930 to 0.945 g/cm<sup>3</sup> for use in the present invention is preferably 1.0 to 3.0 in Mw/Mn. The copolymer then gives a film of high transparency. Mw stands for weight average molecular weight, and Mn for number average molecular weight.

#### BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is an enlarged view in vertical section showing a multilayer film embodying the invention;

FIG. 2 is an enlarged view in vertical section showing another multilayer film embodying the invention;

FIG. 3 includes diagrams for illustrating stepwise an example of process for producing containers having a plurality of chambers and embodying the invention; and

FIG. 4 includes diagrams for illustrating stepwise another example of process for producing containers having a plurality of chambers and embodying the invention.

#### BEST MODE OF CARRYING OUT THE INVENTION

With reference to FIG. 1, the medical multilayer film embodying the present invention comprises an inner layer 1, intermediate layer 2 and outer layer 3. The inner layer 1 is the innermost layer to be in contact with the solid or liquid medicinal preparation to be accommodated in containers formed of the film. The outer layer 3 is the outermost layer to be in contact with the outside air. The intermediate layer 2

includes all layers between the inner layer 1 and the outer layer 3. According to the invention, the intermediate layer 2 is in the form of a single layer (see FIG. 1) or a multiplicity of layers (see FIG. 2).

To enable the inner layer 1 to form an easily peelable seal, this layer is prepared from a resin mixture of ethylene-alpha-olefin copolymer and polypropylene. To give the layer improved heat resistance without impairing the transparency and flexibility thereof, the ethylene-alpha-olefin copolymer to be used has a density which is in the range of 0.930 to 0.945 g/cm<sup>3</sup>. The density is more suitably 0.938 to 0.942 g/cm<sup>3</sup>, most suitably 0.940 to 0.942 g/cm<sup>3</sup>.

The polypropylene to be used can be a propylene homopolymer or a copolymer of propylene and an alpha-olefin.

The copolymer of propylene and alpha-olefin comprises propylene as the main comonomer and contains a specified proportion of alpha-olefin. The copolymer may be in the form of a propylene random copolymer, propylene block copolymer or propylene graft copolymer. Besides ethylene, examples of alpha-olefins present in such copolymers are 1-butene, 1-pentene, 1-hexene, 4-methyl-1-pentene, 1-heptene, 1-octene, 1-nonene, 1-decene, 1-undecene, 1-dodecene and like olefins having 4 to 12 carbon atoms.

Preferably, the copolymer comprises propylene and ethylene.

When the propylene is a copolymer, it is required that the copolymer have nearly the same heat resistance as propylene homopolymer. Accordingly, the proportion of alpha-olefin to be mixed with propylene is relatively small. For example when the alpha-olefin is ethylene, the proportion is up to 20 wt. %, preferably up to 10 wt. %, more preferably up to 5 wt. %. The term "polypropylene" as used hereinafter includes both the homopolymer and the copolymer, unless otherwise stated.

The polypropylene can be 1.0 to 7.0 g/10 min (230 ° C) in melt flow rate (MFR). For example, when the ethylene-alpha-olefin copolymer is about 2.2 g/10 min (190 ° C) in MFR, it is suitable to use a propylene homopolymer which is about 3.0 to about 7.0 g/10 min (230 ° C) in MFR.

According to the present invention, the ethylene-alpha-olefin copolymer having a density in the above-specified range and polypropylene having relatively high compatibility with the copolymer are used to obtain a generally uniform mixture of these resins. This makes it possible to obtain an inner layer which is excellent in properties to form easily peelable seal portion and to prepare a product having an easily peelable seal portion which is openable with a stabilized force.

The resin mixture of polypropylene and ethylene-alpha-olefin copolymer has a wide sealing temperature range permitting formation of easily peelable seal portions and is almost free of the influence of variations in atmospheric temperature at the sealing work site, so that seal strength is readily available always with good stability. Moreover, even if the resin mixture is heated for sterilization of the container with high-pressure steam or with hot water under a high temperature condition (e.g., 121 ° C for 20 minutes), the ethylene-alpha-olefin copolymer with a density of 0.930 to 0.945 g/cm<sup>3</sup> and polypropylene constituting the mixture exhibit high heat resistance, have a high melting point and remain unmelted, with the result that the easily peelable seal portion retains easily peelable seal properties without exhibiting an increased seal strength.

The mixing ratio of ethylene-alpha-olefin copolymer to polypropylene further influences the sealing properties and openability of the easily peelable seal portion. A good result is obtained when the mixing ratio (by weight) of the former to the latter is 1:2 to 3:1, especially 2:3 to 2:1. If the amount of polypropylene mixed is less than the above range, impaired openability will result. Alternatively if it is over the above range, the sealing properties become insufficient, hence an undesirable result. The thickness of the inner layer 1 to be determined is in the range of about 10 to about 50 μm, preferably 25 to 35 μm, so as not to impair the transparency and flexibility. The thickness is up to about 50%, preferably about 5 to about 25%, of the overall thickness of the multilayer film.

For the intermediate layer 2 to retain unimpaired transparency and flexibility and to impart flexibility and impact resistance to the overall film, this layer is prepared from a resin mixture of ethylene-alpha-olefin copolymer with a density of 0.920 to 0.945 g/cm<sup>3</sup> and ethylene-alpha-olefin elastomer with a density of 0.880 to 0.890 g/cm<sup>3</sup> in a mixing ratio of 1:5 to 2:1, preferably 2:5 to 1:2, more preferably 3:7. Especially suitable to use is a mixture comprising a linear polymer. The density of the ethylene-alpha-olefin copolymer, as well as that of the ethylene-alpha-olefin elastomer, is suitably determined from the above range in accordance with the purpose of use. For example, to give further improved heat resistance to the overall film of the invention, the ethylene-alpha-olefin copolymer to be used has a density of 0.930 to 0.945 g/cm<sup>3</sup>, preferably 0.938 to 0.942 g/cm<sup>3</sup>, more preferably 0.940 to 0.942 g/cm<sup>3</sup>.

On the other hand, the ethylene-alpha-olefin elastomer to be used is preferably 0.883 to 0.887 g/cm<sup>3</sup>, more preferably 0.885 g/cm<sup>3</sup>, in density to impart improved flexibility to the overall film.

The resin mixture to be used is suitably up to about 0.910 g/cm<sup>3</sup>, especially preferably 0.900 to 0.910 g/cm<sup>3</sup>, in density.

The intermediate layer 2, which may be a single layer as described above, may alternatively be of a multilayer structure comprising the above resin layer and another resin layer, for example, other resin layer 2a formed in an intermediate portion of the intermediate layer 2 as shown in FIG. 2. To give further improved heat resistance, the resin to be used for the other resin layer 2a is desirably an ethylene-alpha-olefin copolymer having a density of 0.930 to 0.945 g/cm<sup>3</sup>, preferably 0.938 to 0.942 g/cm<sup>3</sup>, more preferably 0.940 to 0.942 g/cm<sup>3</sup>. It is desirable that the layer 2a be inserted in the middle of the intermediate layer and have a thickness which is up to 15% of the thickness of the overall intermediate layer.

The overall thickness of the intermediate layer 2 to be determined suitably is in the range of about 70 to about 150  $\mu$ m, preferably about 80 to about 140  $\mu$ m, more preferably about 110 to about 140  $\mu$ m so as to be about 40 to about 85%, preferably about 45 to about 80%, more preferably about 60 to about 80%, of the overall thickness of the multilayer film.

The outer layer 3, which needs to be transparent and flexible, must have durability to withstand the temperature condition of heat sterilization, for example, high-pressure steam sterilization or hot water sterilization at 121 ° C for 20 minutes. The resin to be used and the structure are as follows. It is suitable to use an ethylene-alpha-olefin copolymer which has a density in the range of 0.930 to 0.945 g/cm<sup>3</sup>, preferably 0.938 to 0.942 g/cm<sup>3</sup>, more preferably 0.940 to 0.942 g/cm<sup>3</sup>. Among such copolymers, a linear polymer is more suitable to use. The thickness of the outer layer 3 to be determined is in the range of about 15 to about 65  $\mu$ m, more preferably 20 to 35  $\mu$ m, and is up to about 40%, more preferably about 5 to about 25%, of the overall thickness of the multilayer film.

The multilayer film of the present invention is produced by the water-cool or air-cool coextrusion blown tubular inflation process, coextrusion T-die process, lamination process or like known process. It is especially desirable to employ the coextrusion process, which forms a resin extrudate of uniform thickness with an improved efficiency and is less likely to deteriorate the resin during extrusion, consequently permitting the layers to retain their respective characteristics and giving a product of high transparency and high flexibility. Further when formed by the coextrusion process, the resin mixture layer is in the form of a generally uniform mixture, which enables the layer to exhibit in its entirety the characteristics of the resin components. The multilayer film is in the form of a tube or sheet. The temperature condition for production is 150 to 270 ° C, preferably 165 to 230 ° C. Since the layers 1, 2 and 3 contain an ethylene-alpha-olefin copolymer as a common component, the layers can be bonded to one another by fusion readily when made into a multilayer film. It is desired that the resins forming the respective layers be reduced in the difference in melt flow rate (MFR) therebetween so as to be uniform in thickness and extrudability. Further with the multilayer film of the invention, one layer may be made in the form of at least two divided layers as prepared by coextrusion. This further improves the overall film in transparency and flexibility.

In this case, the two layers are made of the same resin and are therefore handled as a single layer even if in the form of a multilayer extrudate.

Preferably, the ethylene-alpha-olefin copolymer to be present in the respective layers has a density of 0.930 to 0.945 g/cm<sup>3</sup>, especially a density value close to 0.945 g/cm<sup>3</sup>, since this reduces the content of low-molecular-weight substances in the resin. When the ethylene-alpha-olefin copolymer used is 1.0 to 3.0 in Mw/Mn, the low-molecular-weight substance content of the resin is further reduced. Further when the polypropylene used has a reduced MFR value (230 ° C), the amount of low-molecular-weight substances is still smaller. However, it is desired to reduce the MFR value (230 ° C) to an extent not to impair the flexibility. Use of these resins diminishes an interaction between antibiotics and the low-molecular-weight substance in the resin to obviate the adverse reaction. Accordingly, the low-molecular-weight substance need not be removed by a treatment, i.e., by preheating the resin material in a vacuum or maintaining the material in a vacuum during formation of film or using n-hexane or hot water for extraction or washing. This lowers the production equipment cost.

According to the invention, the heat resistance, transparency and flexibility possessed by the layers 1, 2 and 3 give high heat resistance, transparency and flexibility to the film in its entirety. The intermediate layer 2 and the outer layer 3 give excellent impact resistance, while the inner layer 1 affords excellent easily peelable sealing properties. Thus, the present invention provides a medical multilayer film which is outstanding in heat resistance, transparency, impact resistance and easily peelable sealing properties. Since ethylene-alpha-olefin copolymer is used for the outer layer, the multilayer film of the invention has the advantage that for example when a cover of multilayer barrier film (having an inner layer of ethylene-alpha-olefin copolymer) is to be attached to the outer side of the present film by fusion, the cover can be readily bonded thereto thermally.

The multilayer film of the present invention also provides a medical container having a plurality of chambers which are partitioned by an easily peelable seal or the like for individually accommodating medicinal preparations which are likely to change with time if mixed together, such that the preparations

can be mixed together or made into a solution when to be used. Like the multilayer film of the invention, the container obtained is excellent in heat resistance, transparency, flexibility, impact resistance and easily peelable sealing properties.

The medicinal preparations to be enclosed in the container having a plurality of chambers may be powdery, liquid or solid. Examples of powdery preparations are substances which are hygroscopic or susceptible to oxidation or thermal degradation, such as antibiotics, anticancer agents, steroid agents, fibrinolytic agents, vitamins, etc. Examples of liquid preparations are physiological saline, glucose solutions, distilled water for injection, electrolytic solutions, amino acid solutions, emulsions of fats, etc.

Using the multilayer film of the invention, containers having a plurality of chambers are produced, for example, by the following process. FIG. 3 shows stepwise an example of process for producing such containers. A container A having a plurality of chambers can be obtained by successively executing the following steps (a) to (e).

Step (a): A tubular multilayer film 4 obtained by the blown tubular process is sealed at a fusing temperature of 155 to 185° C to provide container peripheral portions (strong seal portions 5), and is also sealed at a fusing temperature of 105 to 150° C to form easily peelable seal portions (weak seal portions 6) approximately at the central portion of each container to be formed, whereby a multiplicity of container blanks 8a are prepared which are arranged in rows horizontally and vertically.

Step (b): The container blanks 8a are cut off from the multilayer film 4 after sealing, and a container body 8 having a port 7 for attaching a port member is prepared from each of the blanks 8a.

Step (c): The port member 9 is inserted into the port 7 of the container body 8 and attached to the body by fusing means.

Step (d): A cap 10 is attached to an outer opening portion of the port member 9 by fusing means to close the container body.

Step (e): A peel seal 11 which is easily removable is attached to an outer opening portion of the cap 10 by fusing means to obtain a container A having a plurality of chambers.

For example in the case where highly reactive medicinal liquid preparations are to be enclosed individually in upper and lower container portions which are partitioned by the easily peelable seal portions (weak seal portions 6), a highly reactive medicinal liquid preparation 12 is filled into one of the container portions through the port member 9 in the state shown in FIG. 3, (c), followed by the above steps (d) to (e). The container is now in the state shown in FIG. 3, (f). As shown in FIG. 3, (g), the seal portion of the empty chamber is cut to form a filling opening 13. A highly reactive medicinal liquid preparation 14 is filled into the chamber through the opening 13, which is thereafter sealed off, followed by heat sterilization with high-pressure steam or hot water. After the sterilization, the container is externally dried and adjusted to a predetermined shape. FIG. 3, (h) shows the container in this state.

On the other hand, for example when a medicinal preparation such as an antibiotic and a medicinal preparation such as a dissolving liquid are to be enclosed individually in the upper and lower container portions, the dissolving liquid 15 is filled into one of the container portions through the port member 9 in the state shown in FIG. 3, (c), followed by the steps (d) to (e). The container is sterilized with high-pressure steam or hot water in the state shown in FIG. 3, (f), thereafter externally dried, and cut at the seal portion of the empty chamber as seen in FIG. 3, (g) to form a filling opening 13. Clean air is forced into the chamber through the opening 13 for drying, the antibiotic or like medicinal preparation 16 is filled into the chamber through the opening 13 under an aseptic condition, the filling opening 13 is thereafter sealed off, and the container is adjusted to a predetermined shape. FIG. 3, (i) shows the container in this state.

FIG. 4 shows stepwise another example of process for producing containers having a plurality of chambers. Such containers A' can be obtained by successively executing the following steps (a') to (e').

Step (a'): A multilayer film is cut to a piece of film 4' having a specified size, and an aperture 5' for an opening member 6' is formed in the center of the film 4'.

Step (b'): The opening member 6' is attached to the apertured portion 5' of the film 4' on the outer layer side thereof by fusing means.

Step (c'): The film 4' is folded in two with the opening member 6' positioned in the center.

Step (d'): The film 4' as folded in two is sealed along the peripheral portion except at filling openings 7', 8' at a fusing temperature of 155 to 185° C to form strong seal portions 9' and prepare a container body.

Step (e'): An easily peelable seal portion (weak seal portion) 10' is formed at an intermediate portion of the container body at a fusing temperature of 105 to 150° C to obtain a container A' having a plurality of chambers.

For example in the case where highly reactive medicinal liquid preparations are to be filled separately into the respective upper and lower container portions which are partitioned by the easily peelable seal

portion 10', the medicinal liquid preparations 11', 12' are filled into the upper and lower container portions through the filling openings 7', 8', which are then sealed off, followed by sterilization with high-pressure steam or hot water. The container is thereafter externally dried and adjusted to a predetermined shape. FIG. 4, (f') shows the container in this state.

- 5 On the other hand, for example when a medicinal preparation such as an antibiotic and a medicinal preparation such as a dissolving solution are to be enclosed in the upper and lower container portions, the dissolving solution 13' is filled into the liquid chamber through the filling opening 7' therefor in the state shown in FIG. 4, (e'), the two filling openings 7', 8' are thereafter sealed off, and the container is sterilized with high-pressure steam or hot water. FIG. 4, (g') shows the container in this state. The container is  
10 externally dried after the sterilization, the opening 8' for the empty chamber is opened again by cutting as shown in FIG. 4, (g'), and clean air is forced into the chamber through the opening for drying. As shown in FIG. 4, (h'), the antibiotic or like medicinal preparation 14' is filled into the chamber through the reopened opening 8' under an aseptic condition, the filling opening 8' is thereafter sealed off as shown in FIG. 4, (i'), and the container is adjusted to a predetermined shape to complete the filling operation.
- 15 Examples are given below in which medical multilayer films and containers of the invention were prepared. Further given are examples in which these products were tested.

#### Example 1

- 20 Using a water-cooled coextrusion blown tubular machine, a three-layer film was prepared which had an inner layer, intermediate layer and outer layer. The inner layer was a 30- $\mu$ m-thick layer of resin mixture of a linear medium-density polyethylene (ethylene-1-butene copolymer, product of Mitsui Petrochemical Industries, Ltd., 0.941 g/cm<sup>3</sup> in density, 2.2 g/10 min (190° C) in MFR, 2.4 in Mw/Mn, hereinafter referred to as "PE (1)") and a propylene homopolymer (product of Mitsui Petrochemical Industries, Ltd., 0.910 g/cm<sup>3</sup> in density, 4.0 g/10 min (230° C) in MFR, (TAFMER hereinafter referred to as "PP (1)") in a mixing ratio of  
25 3:2. The intermediate layer was a 115- $\mu$ m-thick layer of resin mixture of PE (1) and an ethylene-alpha-olefin elastomer (ethylene-1-butene copolymer, product of Mitsui Petrochemical Industries, Ltd. with the brand name "A," 0.885 g/cm<sup>3</sup> in density, 0.5 g/10 min (190° C) in MFR, hereinafter referred to as "PE (2)") in a mixing ratio of 3:7. The outer layer was a 30- $\mu$ m-thick layer of PE (1). Containers having a plurality of  
30 chambers were prepared from the film by the above process wherein the sealing temperature was 158° C for forming strong seal portions or 140° C for forming weak seal portions. The containers were 100 ml in capacity and formed with easily peelable seal portions.

#### Examples 2-8 and Comparative Examples 1 and 2

- 35 The following multilayer films and containers having a plurality of chambers were prepared in the same manner as in Example 1.

The films used for comparative tests were a two-layer resin film having the same structure as described with reference to the prior art, and a three-layer film different from those of the invention.

40

#### Example 2

- Inner layer: resin mixture of PE (1) + PP (1) (2:1 in mixing ratio)  
Intermediate layer: resin mixture of PE (1) + PE (2) (3:7 in mixing ratio)  
45 Outer layer: PE (1)

#### Example 3

- Inner layer: resin mixture of PE(1) + PP (1) (1:1 in mixing ratio)  
50 Intermediate layer: resin mixture of PE(1) + PE (2) (3:7 in mixing ratio)  
Outer layer: PE (1)

#### Example 4

- 55 Inner layer: resin mixture of PE (1) + PP (1) (2:3 in mixing ratio)  
Intermediate layer: resin mixture of PE (1) + PE (2) (3:7 in mixing ratio)  
Outer layer: PE (1)



Example 5

Inner layer: resin mixture of PE (1) + PP (1) (3:2 in mixing ratio)  
Intermediate layer  
5 First layer: resin mixture of PE (1) + PE (2) (3:7 in mixing ratio)  
Second layer: PE (1)  
Third layer: resin mixture of PE (1) + PE (2) (3:7 in mixing ratio)  
Outer layer: PE (1)

10 Example 6

Inner layer: resin mixture of PE (1) + PP (1) (3:2 in mixing ratio)  
Intermediate layer: resin mixture of PE(1) + PE (2) (3:7 in mixing ratio)  
Outer layer: PE (1)

15

Example 7

Inner layer: resin mixture of PE (1) + PP (1) (3:2 in mixing ratio)  
Intermediate layer: resin mixture of PE (1) + PE (2) (3:7 in mixing ratio)  
20 Outer layer: PE (1)

Example 8

Inner layer: resin mixture of PE (1) + PP (1) (3:2 in mixing ratio)  
25 Intermediate layer: resin mixture of PE (1) + PE (2) (3:7 in mixing ratio)  
Outer layer: PE (1)

Comparative Example 1

30 Inner layer: resin mixture of PE (3) + PP (2) (2:1 in mixing ratio)  
PE (3): linear low-density polyethylene (ethylene-1-butene copolymer, product of Mitsui Petrochemical Industries, Ltd., 0.920 g/cm in density, 2.0 g/10 min (190 ° C) in MFR, hereinafter referred to as "PE (3)")  
PP (2): propylene random copolymer (ethylene-propylene copolymer, product of Mitsui Petrochemical Industries, Ltd., 0.910 g/cm<sup>3</sup> in density, 1.0 g/10 min (230 ° C) in MFR, hereinafter referred to as "PP (2)")  
35 Outer layer: PE (3)

Comparative Example 2

Inner layer: resin mixture of PE (4) + PP (2) (3:2 in mixing ratio)  
40 PE (4): linear high-density polyethylene (ethylene-1-butene copolymer, product of Mitsui Petrochemical Industries, Ltd., 0.961 g/cm<sup>3</sup> in density, 17 g/10 min (190 ° C) in MFR, hereinafter referred to as "PE (4)")  
Intermediate layer: resin mixture of PE (1) + PE(2) (3:7 in mixing ratio)  
Outer layer: PE (1)

45 Test Examples

The containers prepared in Examples 1 - 8 of the invention and Comparative Examples 1 and 2 were filled with distilled water in an amount of 50 ml in each of the chambers, then sterilized with hot water at 121 ° C for 20 minutes and thereafter evaluated by the following test methods. Tables 1 and 2 below show the results.

50

For a heat resistance test, the container as sterilized was visually checked for deformation, rupture, leakage through the seal portions, creases and blocking as standards for the evaluation of heat resistance.

To evaluate transparency, the container was visually checked for white turbidity after the sterilization.

For the evaluation of flexibility, the enclosed liquid was allowed to spontaneously discharge from the container at room temperature from a height of 60 cm, and the container was visually observed.

55

To conduct a drop test for the evaluation of impact resistance, 10 containers held at a temperature of up to 5 ° C were packed into a box (105 mm in width, 125 mm in length, 185 mm in height, 160 g in weight), and three such boxes were prepared. Each box was then allowed to fall from a position 1.2 m

# EP 0 635 254 A1

above the floor to give the impact of fall 10 times to each of sides, edges and corners of the box. After the three boxes were all subjected to the impact, the 30 containers were taken out from the boxes and each visually checked for cracking or rupture (according to JIS-Z-0202).

A compression test was conducted to evaluate the openability of the easily peelable seal portion. A compression jig, 100 mm in diameter, was attached to a tensile compression tester, STROGRPH MZ, product of Toyo Seiki Seisakusho Co., Ltd, and the liquid enclosing portion was pressed by the jig at a rate of 50 mm/min to measure the pressure applied to the jig when the easily peelable seal portion was opened for the determination of variation coefficient of opening forces. The initial force applied for opening the easily peelable seal portion was determined from the range of 10 to 25 kg in accordance with the inner layer resin structure concerned. The opening force variation coefficient relatively represents variations in the easily peelable seal portion opening force, and was calculated from the following equation.

Opening force variation coefficient

$$= \frac{\text{Standard deviation of opening forces}}{\text{Average of opening forces}}$$

Additionally, the appearance of the entire container was visually checked for creases, deformation and rupture.

Overall evaluation was made based on the foregoing items of evaluation.

Table 1

	Thickness of outer layer (μ)	Thickness of intermediate layer (μ)			Thickness of inner layer (μ)	Overall thickness (μ)
Ex. 1	PE 1 30μ	PE 1 + PE 2 115μ			PE 1 + PP 1 30μ	175μ
Ex. 2	PE 1 30μ	PE 1 + PE 2 115μ			PE 1 + PP 1 30μ	175μ
Ex. 3	PE 1 30μ	PE 1 + PE 2 115μ			PE 1 + PP 1 30μ	175μ
Ex. 4	PE 1 30μ	PE 1 + PE 2 115μ			PE 1 + PP 1 30μ	175μ
Ex. 5	PE 1 20μ	PE 1 + PE 2 60μ	PE 1 10μ	PE 1 + PE 2 60μ	PE 1 + PP 1 25μ	175μ
Ex. 6	PE 1 30μ	PE 1 + PE 2 125μ			PE 1 + PP 1 30μ	185μ
Ex. 7	PE 1 65μ	PE 1 + PE 2 80μ			PE 1 + PP 1 30μ	175μ
Ex. 8	PE 1 50μ	PE 1 + PE 2 95μ			PE 1 + PP 1 30μ	175μ
Comp. Ex. 1	PE 3 125μ				PE 3 + PP 2 50μ	175μ
Comp. Ex. 2	PE 1 30μ	PE 1 + PE 2 115μ			PE 4 + PP 2 30μ	175μ

Table 2

	Drop test (number of ruptured containers)	Spontaneous dischargeability	Transparency	Compression test	Heat resistance	Appearance	Overall evaluation
Ex. 1	⊙ (0/30)	⊙	⊙	⊙	⊙	⊙	⊙
Ex. 2	⊙ (0/30)	⊙	⊙	⊙	⊙	⊙	⊙
Ex. 3	⊙ (0/30)	⊙	⊙	⊙	⊙	⊙	⊙
Ex. 45	⊙ (0/30)	⊙	⊙	⊙	⊙	⊙	⊙
Ex. 5	⊙ (0/30)	⊙	⊙	⊙	⊙	⊙	⊙
Ex. 6	⊙ (0/30)	⊙	⊙	⊙	⊙	⊙	⊙
Ex. 7	⊙ (0/30)	⊙	○	⊙	⊙	○	⊙
Ex. 8	⊙ (0/30)	⊙	○	⊙	⊙	○	⊙
Compl.0 Ex. 1	*	*	X	*	X	X	X
Comp. Ex. 2	X (10/30)	X	X	Δ	⊙	Δ	Δ

In Table 2, the symbol ⊙ stands for "excellent," ○ for "good", Δ for "poor" and X for "unacceptable."

The test results given above (Table 2) will further be described in detail.

With respect to the opening force variation coefficient of the easily peelable seal portion obtained by the compression test, the containers of Examples 1 to 8 of the invention were 0.068 to 0.150, whereas the containers of Comparative Example 2 were 0.410, which represents great variations in the opening force.

The containers of Comparative Example 1 were insufficient in heat resistance, therefore failed to withstand sterilization at 121° C for 20 minutes, melted and were unable to remain in shape. For this reason, it was impossible to conduct the drop test, spontaneous dischargeability test and compression test for the containers as indicated by the mark \*.

5 Containers which were the same as those of Examples 1 to 8 were tested under the same conditions as above except that the density of PE (1) was altered from 0.941 g/cm<sup>3</sup> to 0.940 g/cm<sup>3</sup> (2.2 g/10 min (190° C) in MFR, 2.4 in Mw/Mn), whereby substantially the same results as those achieved by Examples 1 to 8 were obtained.

10 While a propylene random copolymer was used as PP (2) in Comparative Examples 1 and 2, the same results as above were obtained when PP (1) was used in place of PP (2).

Thus, the present invention provides medical multilayer films which are outstanding in heat resistance, transparency, flexibility, impact resistance and easily peelable sealing properties. Use of these films further provides medical containers having a plurality of chambers and excellent in heat resistance, transparency, flexibility, impact resistance and easily peelable sealing properties.

15

### Claims

1. A medical multilayer film characterized in that the film comprises an inner layer, an intermediate layer and an outer layer each made primarily of a polyolefin,  
 20 the inner layer being formed of resin mixture of an ethylene-alpha-olefin copolymer having a density of 0.930 to 0.945 g/cm<sup>3</sup> and a polypropylene,  
 the intermediate layer including at least one resin mixture layer of resin mixture of an ethylene-alpha-olefin copolymer having a density of 0.920 to 0.945 g/cm<sup>3</sup> and an ethylene-alpha-olefin elastomer having a density of 0.880 to 0.890 g/cm<sup>3</sup> in a mixing ratio by weight of 1:5 to 2:1, the resin mixture layer having a thickness of at least 85% of the overall thickness of the intermediate layer, and  
 25 the outer layer being formed of an ethylene-alpha-olefin copolymer having a density of 0.930 to 0.945 g/cm<sup>3</sup>.
2. A medical multilayer film as defined in claim 1 wherein the ethylene-alpha-olefin copolymer of the intermediate layer has a density of 0.930 to 0.945 g/cm<sup>3</sup>.
3. A medical multilayer film as defined in claim 1 or 2 wherein the intermediate layer consists singly of the resin mixture layer.
- 35 4. A medical multilayer film as defined in claim 1 or 2 wherein the intermediate layer has a multilayer structure comprising the resin mixture layer and other resin layer formed at an intermediate portion of the layer, the other resin layer being made of an ethylene-alpha-olefin copolymer having a density of 0.930 to 0.945 g/cm<sup>3</sup>.
- 40 5. A medical multilayer film as defined in claim 1 wherein the ethylene-alpha-olefin copolymer used in each of the inner layer, the intermediate layer and the outer layer is 0.938 to 0.942 g/cm<sup>3</sup> in density.
6. A medical multilayer film as defined in claim 1 wherein the ethylene-alpha-olefin copolymer used in each of the inner layer, the intermediate layer and the outer layer is 0.940 to 0.942 g/cm<sup>3</sup> in density.
- 45 7. A medical multilayer film as defined in claim 1 or 2 wherein the ethylene-alpha-olefin elastomer used in the intermediate layer is 0.883 to 0.887 g/cm<sup>3</sup> in density.
8. A medical multilayer film as defined in claim 1 or 2 wherein the ethylene-alpha-olefin copolymer and the ethylene-alpha-olefin elastomer serving as the components of the resin mixture layer for use in the intermediate layer are in a mixing ratio by weight of 2:5 to 1:2.
- 50 9. A medical multilayer film as defined in claim 1 or 2 wherein the ethylene-alpha-olefin copolymer and the ethylene-alpha-olefin elastomer serving as the components of the resin mixture layer for use in the intermediate layer are in a mixing ratio by weight of 3:7.
- 55 10. A medical multilayer film as defined in claim 4 wherein the intermediate layer has in the middle thereof the other resin layer of an ethylene-alpha-olefin copolymer having a density of 0.938 to 0.942 g/cm<sup>3</sup>.

11. A medical multilayer film as defined in claim 4 wherein the intermediate layer has in the middle thereof the other resin layer of an ethylene-alpha-olefin copolymer having a density of 0.940 to 0.942 g/cm<sup>3</sup>.
- 5 12. A medical multilayer film as defined in claim 1 or 2 wherein the ethylene-alpha-olefin copolymer and the polypropylene for use in forming the inner layer are in a mixing ratio by weight of 2:3 to 2:1.
- 10 13. A medical multilayer film as defined in claim 1 wherein the ethylene-alpha-olefin copolymer used for each of the inner layer, the intermediate layer, and the outer layer is 0.940 to 0.942 g/cm<sup>3</sup> in density, the ethylene-alpha-olefin elastomer used for the intermediate layer is 0.883 to 0.887 g/cm<sup>3</sup> in density, and the ethylene-alpha-olefin copolymer and the ethylene-alpha-olefin elastomer serving as the components of the resin mixture layer for use in the intermediate layer are in a mixing ratio by weight of 3:7.
- 15 14. A medical multilayer film as defined in claim 4 wherein the ethylene-alpha-olefin copolymer for use in each of the inner layer, the intermediate layer, the other layer and other layer to be formed at an intermediate portion of the intermediate layer is 0.940 to 0.942 g/cm<sup>3</sup> in density, the ethylene-alpha-olefin elastomer for use in the intermediate layer is 0.883 to 0.887 g/cm<sup>3</sup> in density, and the ethylene-alpha-olefin copolymer and the ethylene-alpha-olefin elastomer serving as the components of the resin mixture layer for use in the intermediate layer are 3:7 in mixing ratio by weight.
- 20 15. A medical multilayer film as defined in claim 1 or 2 wherein the polypropylene for use in the inner layer is a propylene homopolymer.
- 25 16. A medical multilayer film as defined in claim 1 or 2 wherein the polypropylene for use in the inner layer is a copolymer of an alpha-olefin and propylene serving as the main comonomer.
- 30 17. A medical container having a plurality of chambers and formed of a medical multilayer film as defined in claim 1 or 2.
18. A medical container having a plurality of chambers and formed of a medical multilayer film as defined in claim 13.
- 35 19. A medical container having a plurality of chambers and formed of a medical multilayer film as defined in claim 14.

FIG. 1

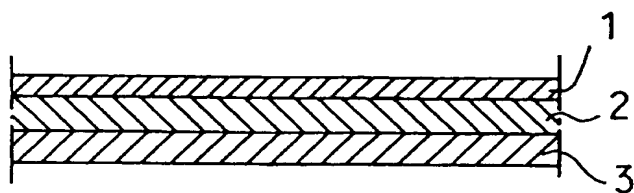


FIG. 2

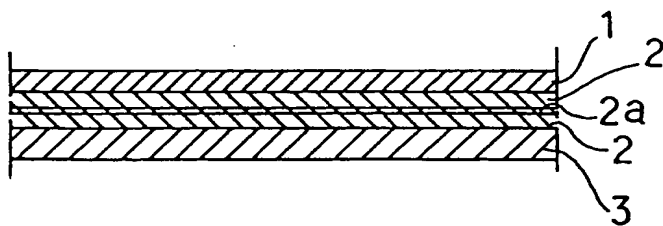


FIG. 3

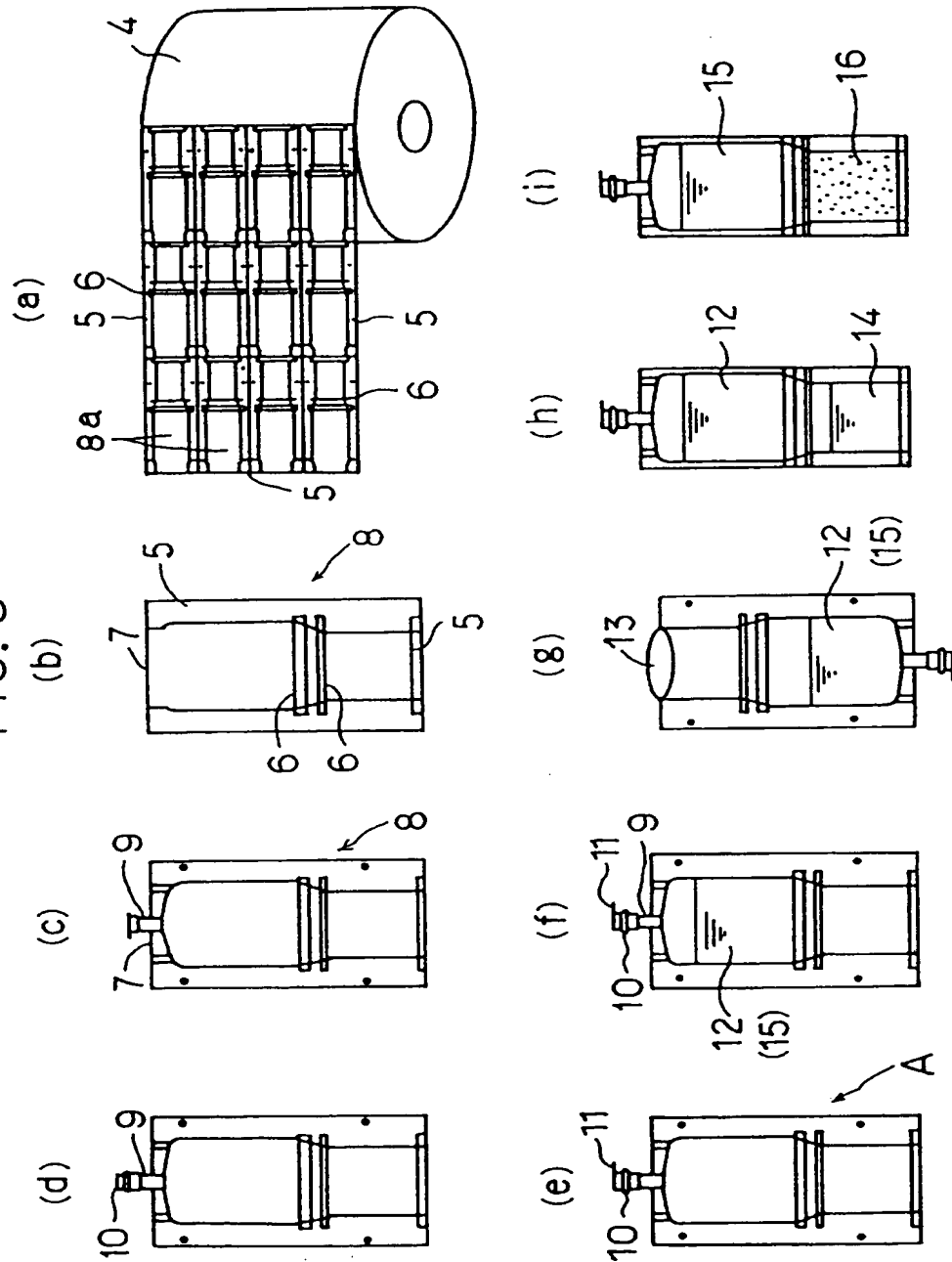
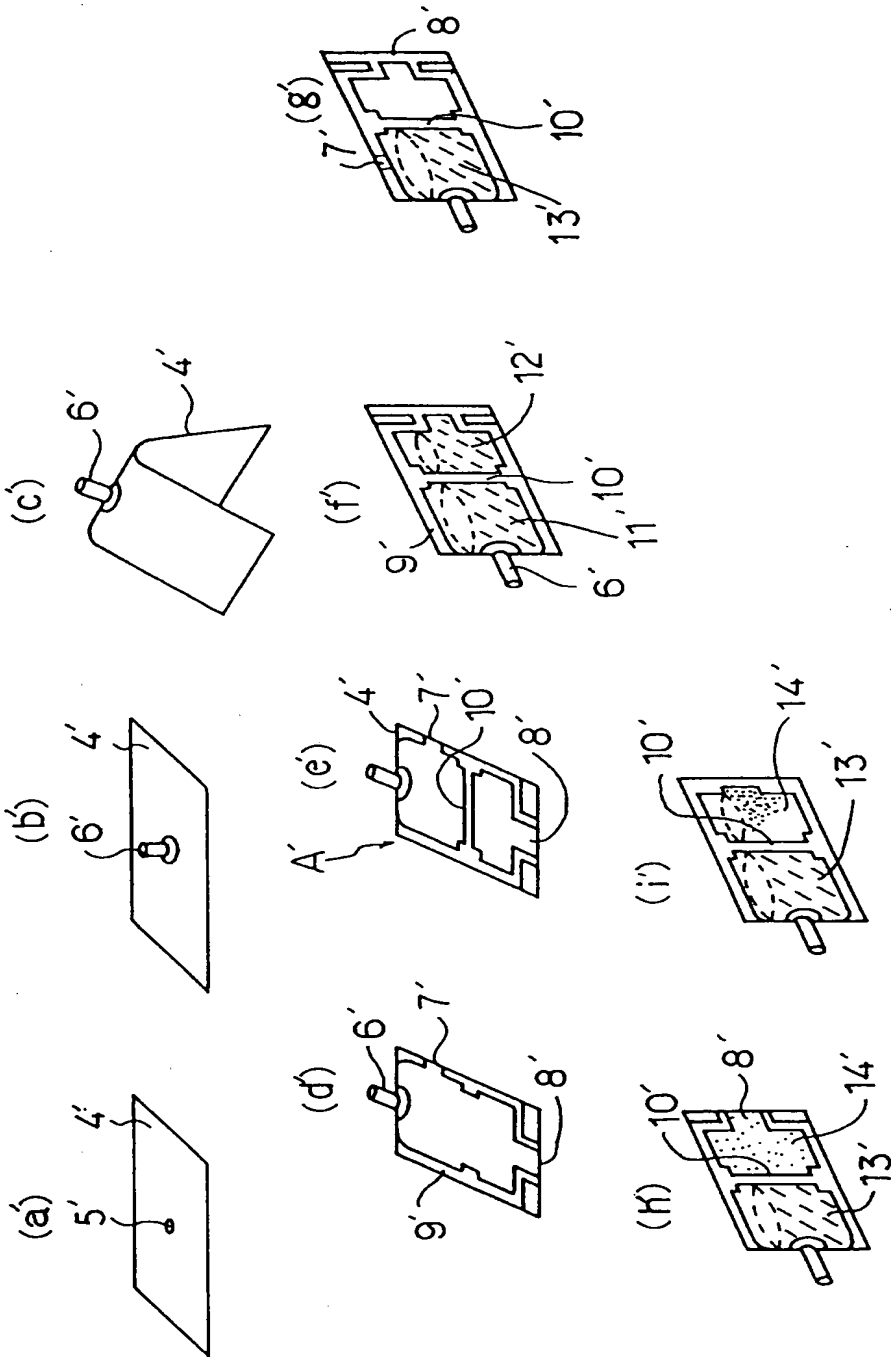


FIG. 4





# INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP94/00143

## A. CLASSIFICATION OF SUBJECT MATTER

Int. Cl<sup>5</sup> A61J1/05

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Int. Cl<sup>5</sup> A61J1/05

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Jitsuyo Shinan Koho 1926 - 1994

Kokai Jitsuyo Shinan Koho 1971 - 1994

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	JP, A, 1-240469 (Shin Sozai Sogo Kenkyusho K.K.), September 26, 1989 (26. 09. 89), Claim	1-19
A	JP, A, 4-242647 (Roussel Morishita Co., Ltd.), August 31, 1992 (31. 08. 92), Claim	1-19
A	JP, U, 5-5138 (Otsuka Pharmaceutical Factory, Inc.), January 26, 1993 (26. 01. 93), Claim	1-19

☐ Further documents are listed in the continuation of Box C.

☐ See patent family annex.

\* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"Z" document member of the same patent family

Date of the actual completion of the international search

April 26, 1994 (26. 04. 94)

Date of mailing of the international search report

May 17, 1994 (17. 05. 94)

Name and mailing address of the ISA/

Japanese Patent Office

Facsimile No.

Authorized officer

Telephone No.